

## COOPERATIVE STUDIES

# Blood Pressure in Survivors of Myocardial Infarction

THE CORONARY DRUG PROJECT RESEARCH GROUP\*

The prognostic significance of blood pressure elevation and its associated characteristics in patients recovered from myocardial infarction was studied in the placebo group ( $n = 2,789$ ) of the Coronary Drug Project. Age, relative body weight, heart rate and ST depression on the electrocardiogram were important positive correlates of hypertension measured at baseline. The relation of uric acid and elevated plasma glucose levels to increased blood pressure could be partially explained as side effects of thiazide diuretic therapy. A "high normal" baseline blood pressure best predicted the development of hypertension among survivors of myocardial infarction. Both combined systolic and diastolic hyper-

tension and isolated systolic hypertension were adverse prognostic factors.

Changes in blood pressure, including the prognostic implications of a decrease in pressure, were also analyzed in the subset of patients who sustained a recurrent nonfatal myocardial infarction. Decreases in systolic (mean 7.9 mm Hg) and diastolic (mean 3.6 mm Hg) blood pressure were sustained in this subset. Patients whose blood pressure decreased after recurrent myocardial infarction tended to have higher mortality rates than those of comparable patients whose blood pressure increased or remained unchanged.

Hypertension is a major risk factor for initial coronary events, that is, angina, myocardial infarction and sudden cardiac death. This has been documented (1-9) extensively for elevation of both systolic and diastolic blood pressures. Although this relation is well established, little information is available about the clinical significance of systolic and diastolic blood pressure levels in persons *after* recovery from one or more episodes of myocardial infarction. The placebo group in the Coronary Drug Project provided us with the opportunity to study this issue.

*This report addresses the following questions:*

- 1) What are the demographic, clinical, electrocardiographic, biochemical and hematologic correlates of systolic and diastolic hypertension (as measured at baseline) in men recovered from myocardial infarction?
- 2) What variables measured at baseline correlate with

development over time of systolic and diastolic hypertension among survivors of myocardial infarction?

- 3) What is the prognostic significance of baseline systolic and diastolic blood pressure levels for subsequent coronary and cerebrovascular events and survival in patients recovered from myocardial infarction?

- 4) What are the effects of recurrent myocardial infarction on systolic and diastolic blood pressures?

- 5) What is the effect on prognosis of a decrease in blood pressure after a recurrent myocardial infarction?

## Methods

**Study design.** The background, design and organization of the Coronary Drug Project have been described (10-14). Its primary objective was to evaluate the efficacy and safety of several lipid-influencing drugs in the long-term management of men after recovery from myocardial infarction. For this purpose 8,341 men were recruited by the 53 Coronary Drug Project clinical centers and randomly assigned to six treatment groups. Approximately one-third of the patients (2,789 men) were allocated to a placebo group; data from this group of patients form the basis for this report.

**Study patients.** Patients enrolled in the Coronary Drug Project were 30 to 64 year old men (mean age 52.4; 93% white) with a history of one or more electrocardiographically documented episodes of myocardial infarction. Entry into the Coronary Drug Project was limited to patients in New York Heart Association functional class I or II (15) who were free of a specified list of diseases. All patients had had their last myocardial infarction at least 3 months (mean

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= 36) before enrollment and had had no recent worsening of their coronary heart disease or any other major illness. Extensive standardized baseline data (demographic, clinical, electrocardiographic, biochemical and hematologic) were collected for each patient. Baseline measurements were taken before entry into the study, 3 or more months after the qualifying myocardial infarction.

*Appendix A lists the 40 baseline variables from which adjusting variables were chosen.* These included three casual blood pressure determinations at 1 month intervals. The three systolic blood pressure and three diastolic blood pressure measurements were averaged and the mean of each was used as a single baseline variable for each of the 2,789 men randomized to the placebo group. Blood pressure levels were not a basis for exclusion from the study.

*Follow-up.* All men in the Coronary Drug Project were followed up for a minimum of 5 years with clinic visits at 4 month intervals. At the baseline visit and at each annual clinic visit, the patient was instructed to come to the clinic in a fasting state; for nonannual visits a "fat-free" state was required. At each visit, blood pressure was measured with the patient either supine or sitting with the forearm at the level of the heart. Diastolic blood pressure determination used the fifth phase (disappearance of sound) as the criterion (16).

*Data sent to the Coordinating Center included "events"* such as death, recurrent nonfatal myocardial infarction, intermediate coronary episodes, angina pectoris, stroke, intermittent cerebral ischemic attacks and venous thromboembolism. The diagnoses of these events were established by the study clinic physician; diagnostic criteria are given in Appendix B.

**Analyses.** This report analyzes the 5 year follow-up data from several cohorts.

1) *Total cohort.* All 2,789 men randomized to placebo therapy constitute the total cohort. Analysis of the relation of blood pressure to long-term prognosis focuses on three end points: *mortality* from all causes; *recurrent major coronary events* (defined as definite nonfatal myocardial infarction and fatal coronary events) and *combined cerebrovascular events* (defined as the combination of fatal stroke, nonfatal stroke [definite or suspected] and intermittent cerebral ischemic attacks [definite or suspected]).

2) *Normotensive cohort.* The 1,630 men with a baseline systolic blood pressure of less than 140 mm Hg and a baseline diastolic blood pressure of less than 90 mm Hg and who used neither antihypertensive nor diuretic drugs at the baseline visit constitute the normotensive cohort.

3) *Recurrent myocardial infarction cohort.* During the 5 year follow-up period, 347 men sustained definite recurrent nonfatal myocardial infarction and 69 men had suspected recurrent myocardial infarction. These groups were compared with men who did not have recurrent myocardial infarction. A randomly determined follow-up visit was as-

signed for each patient in the comparison group to match the distribution of follow-up visits in the group with definite recurrent myocardial infarction. The criterion that patients must have had a recent premyocardial infarction clinic visit\* for evaluation limited the analyses to 326 men in the *myocardial infarction cohort*, 68 men in the *suspected myocardial infarction cohort* and 1,822 men in the *nonmyocardial infarction cohort*. Additional analyses requiring three visits before and three visits after myocardial infarction further restricted analyses to 186 men in the *myocardial infarction cohort*, 58 men in the *suspected myocardial infarction cohort* and 1,222 men in the *nonmyocardial infarction cohort*.

In all three cohorts, the men not receiving drugs influencing blood pressure (that is, diuretic and nondiuretic antihypertensive medication) at entry into the Coronary Drug Project, called the *no medication cohort*, were subsequently examined separately.

**Blood pressure definitions.** The following criteria were used for blood pressure definitions.

#### *Baseline systolic hypertension.†*

1. Average of three baseline systolic blood pressures of 140 mm Hg or greater and/or either of the following at two of the three baseline visits:
2. Antihypertensive drug (nondiuretic) use
3. Diuretic drug use without digitalis use

#### *Baseline diastolic hypertension.†*

1. Average of three baseline diastolic blood pressures of 90 mm Hg or greater and/or either of the following at two of the three baseline visits:
2. Antihypertensive drug (nondiuretic) use
3. Diuretic drug use without digitalis use

*Development of systolic hypertension.†* Any combination of two or all three of the following at two consecutive follow-up visits within 5 years after entry into the study:

1. Systolic blood pressure of 140 mm Hg or greater
2. Antihypertensive drug (nondiuretic) use
3. Diuretic drug use without digitalis use

*Development of diastolic hypertension.†* Any combination of two or all three of the following at two consecutive follow-up visits within 5 years after entry into the study:

1. Diastolic blood pressure of 90 mm Hg or greater
2. Antihypertensive drug (nondiuretic) use
3. Diuretic drug use without digitalis use (see later)

\*Recent premyocardial infarction clinic visit is defined as that follow-up visit immediately before the recurrent myocardial infarction or one visit earlier if the immediately prior clinic appointment was not kept.

†Defined as 1 if conditions are met, 0 if otherwise.

The inclusion of diuretic use as part of the definition of hypertension makes an assumption that clearly is *not* valid for every Coronary Drug Project patient taking diuretic drugs without digitalis; on occasion such patients could have been treated with diuretic drugs to decrease fluid retention (congestive heart failure) without concomitant use of digitalis; hypertension need not have been present. A definition of hypertension that does not include diuretic drug use does not alter the findings presented in this report (except that the use of diuretic drugs becomes a correlate of hypertension).

To assess further the relation of baseline hypertension to 5 year prognosis, an average level of three baseline systolic blood pressures of 140 mm Hg or greater and an average level of three baseline diastolic blood pressures of 90 mm Hg or greater were used to divide the placebo group of patients into four groups:

**Normotension:** systolic blood pressure less than 140 mm Hg and diastolic blood pressure less than 90 mm Hg.

**Isolated systolic hypertension:** systolic blood pressure of 140 mm Hg or greater and diastolic blood pressure less than 90 mm Hg.

**Isolated diastolic hypertension:** diastolic blood pressure of 90 mm Hg or greater and systolic blood pressure less than 140 mm Hg.

**Combined systolic and diastolic hypertension:** systolic blood pressure of 140 mm Hg or greater and diastolic blood pressure of 90 mm Hg or greater.

**Statistical methods.** The principal statistical method used was linear regression, both univariate and multivariate. Appendix A lists 40 entry characteristics, 19 of which were chosen as adjusting variables. Nineteen other variables (electrocardiographic characteristics, use of medications and history of clinical conditions) were excluded because they were considered a consequence rather than a possible cause of the two elevated blood pressure variables. A *t* value (regression coefficient divided by its standard error) was used to evaluate statistical significance of the regression coefficient. The partial correlation (the correlation of each independent variable with the dependent variable removing the effect of variables already in the equation) and the mul-

tiply *R* (the correlation of the dependent variable with the predicted value) are reported for regression analyses. Student's *t* test for paired observations was used to compare pre- and postmyocardial infarction blood pressure levels.

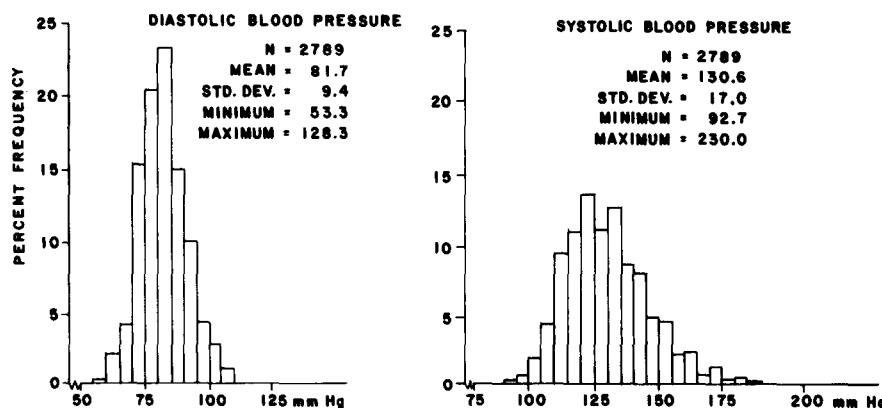
*Multiple response variables and subgroups complicate the interpretation of conventional tests of significance.* Multiple testing increases the probability that one or more comparisons will appear significant by chance alone. For this reason, a result is not considered as statistically significant unless it achieves at least the nominal 1.0% ( $p \leq 0.01$ ) level of significance ( $t \geq 2.58$ ).

## Results

The distribution of baseline systolic and diastolic blood pressure levels for the total cohort of 2,789 men is presented in Figure 1. The distribution of systolic blood pressure was moderately skewed to the right; its coefficient of variation was consequently somewhat greater than that for diastolic blood pressure (13.0 versus 11.5). The mean blood pressure values were 130.6 and 81.7 mm Hg, respectively.

**Correlates of baseline blood pressure (Table 1).** Eleven of the 38 baseline variables (use of antihypertensive drugs, age, 1 hour glucose level, relative body weight, ST depression, use of diuretic drugs, serum uric acid, time since last myocardial infarction, fasting glucose, triglycerides, heart rate on electrocardiogram) in the simple correlation matrix generated for the total cohort had correlation coefficients (*r*) with systolic blood pressure or diastolic blood pressure, or both, of 0.10 or greater and none had *r* values less than -0.10. Most of these significantly positive *r* values also applied to the *no medication cohort*.

**Correlates of baseline systolic and diastolic hypertension (Table 2).** The prevalence of systolic and diastolic hypertension at baseline was 30.6 and 23.7%, respectively. Eight of the baseline variables in the simple correlation matrix generated for the total cohort had correlation coefficients with baseline systolic or diastolic hypertension, or both, of 0.10 or greater and none had correlation coefficients less than -0.10. Because baseline hypertension (as defined)



**Figure 1.** Distribution of baseline (mean of three measurements) systolic and diastolic blood pressures in total cohort of 2,789 men in placebo group. STD. DEV. = standard deviation.

**Table 1.** Simple Correlation Coefficients Between Baseline Systolic and Diastolic Blood Pressure and Other Baseline Characteristics\*

	Simple Correlation Coefficient			
	Total Cohort (n = 2,789)		No Med Cohort (n = 2,216)	
	SBP	DBP	SBP	DBP
Use of antihypertensive drugs	0.322	0.282	N/A	N/A
Age	0.195	-0.013	0.187	-0.016
1 hour glucose	0.175	0.109	0.155	0.089
Relative body weight	0.174	0.236	0.180	0.236
ST depression	0.171	0.090	0.116	0.053
Use of diuretic drugs	0.170	0.163	N/A	N/A
Uric acid	0.136	0.162	0.127	0.130
Time since last myocardial infarction	0.127	0.081	0.124	0.076
Fasting glucose	0.116	0.080	0.096	0.054
Triglycerides	0.092	0.104	0.088	0.107
Heart rate on electrocardiogram	0.091	0.140	0.133	0.177

\*Only variables with coefficients  $\geq 0.10$  with either systolic blood pressure (SBP) or diastolic blood pressure (DBP) in either cohort are included; variables were selected from the other 38 (omitting systolic blood pressure and diastolic blood pressure) baseline characteristics listed in Appendix A. N/A = not applicable.

is a function of baseline blood pressure level, most of these variables correlated with baseline systolic or diastolic blood pressure, or both. Although directly related to baseline systolic hypertension, age did not correlate with baseline diastolic hypertension. Relative body weight and 1 hour glucose correlated with both baseline systolic and diastolic hypertension. The level of serum uric acid showed a strong correlation with both systolic and diastolic hypertension. A correlation between heart rate and diastolic hypertension was present in the *no medication cohort*.

**Correlates of development of systolic and diastolic hypertension (Table 3).** Among the 1,547 men in the normotensive cohort who were present for at least two consecutive follow-up visits, 636 (41.1%) developed systolic hypertension and 520 (33.6%) developed diastolic hyper-

tension during the 5 years of follow-up. The five baseline variables most predictive for the development of systolic and diastolic hypertension, respectively, are listed in Table 3. A "high normal" baseline blood pressure was by far the best independent predictor of the development of future hypertension. There is a strong direct correlation of age with the development of systolic hypertension. Relative body weight was directly correlated with the development of both systolic and diastolic hypertension. Time from last myocardial infarction to entry into the Coronary Drug Project was inversely related to the development of systolic hypertension. Fasting plasma glucose level was inversely associated with the development of diastolic hypertension. There was no correlation with 1 hour glucose level.

The regression coefficients from the five variable regres-

**Table 2.** Simple Correlation Coefficients Between Baseline Systolic and Diastolic Hypertension and Other Baseline Characteristics\*

	Simple Correlation Coefficient			
	Total Cohort (n = 2,789)		No Med Cohort (n = 2,216)	
	SBP: HPT	DBP: HPT	SBP: HPT	DBP: HPT
Age	0.183	0.025	0.182	-0.013
Uric acid	0.169	0.190	0.094	0.090
1 hour glucose	0.161	0.098	0.127	0.060
Relative body weight	0.148	0.181	0.114	0.152
ST depression	0.131	0.080	0.088	0.024
Fasting glucose	0.114	0.069	0.084	0.026
Cardiomegaly	0.110	0.084	0.064	0.028
Time since last myocardial infarction	0.107	0.085	0.101	0.068
Heart rate on electrocardiogram	0.036	0.086	0.080	0.132

\*Only variables with coefficients  $\geq 0.10$  with either systolic hypertension (SBP HPT) or diastolic hypertension (DBP HPT) in either cohort are included; variables were selected from the other 35 (omitting systolic blood pressure, diastolic blood pressure, digitalis use, diuretic drug use, antihypertensive agent use) baseline characteristics listed in Appendix A. Other abbreviations as in Table 1.

**Table 3.** Development of Systolic and Diastolic Hypertension During 5 Years and Relation to Other Baseline Variables: Baseline Normotensive Cohort (n = 1,547)

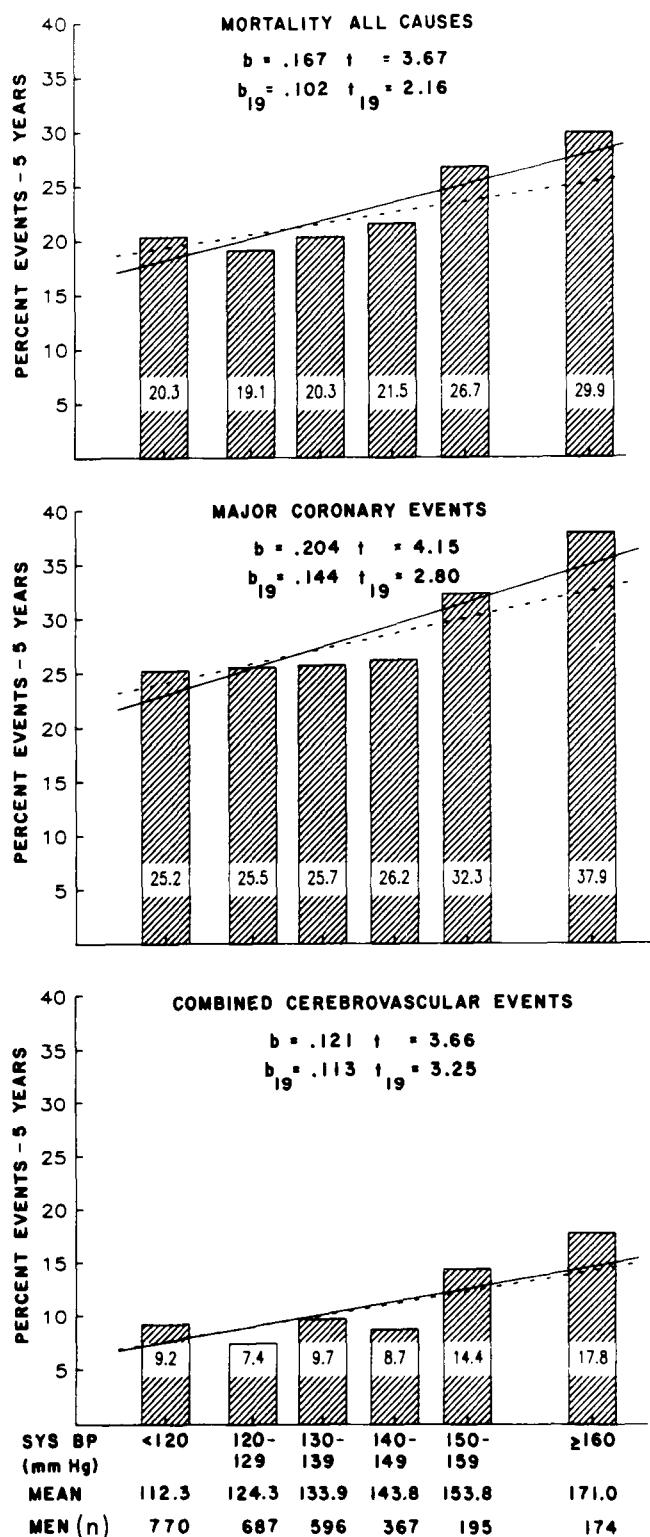
Part 1: Regression and Correlation Coefficients					
Baseline Variable	Simple Correlation Coefficient	Partial Correlation Coefficient	Regression Coefficient		
Development of Systolic Hypertension					
Systolic blood pressure	0.417	0.398	0.02089		
Age	0.160	0.144	0.00915		
Time since last myocardial infarction	0.001	−0.065	−0.01008		
Relative body weight	0.110	0.064	0.21607		
Total bilirubin	−0.066	−0.057	−0.11000		
Intercept			−2.75731		
Mult R = 0.444					
Development of Diastolic Hypertension					
Diastolic blood pressure	0.345	0.198	0.01785		
Systolic blood pressure	0.304	0.120	0.00718		
Relative body weight	0.156	0.101	0.33868		
Fasting glucose	−0.034	−0.061	−0.00138		
White blood count	−0.041	−0.047	−0.00001		
Intercept			−2.09188		
Mult R = 0.381					
Part 2: Observed Event Rate by Quintile of Expected Risk for Development of Systolic and Diastolic Hypertension During 5 Years of Follow-up Calculated From Five Variable Regression Model					
Quintile	Denominator	Systolic Hypertension		Diastolic Hypertension	
		Numerator	Rate	Numerator	Rate
1	309	42	13.6	28	9.1
2	309	73	23.6	71	23.0
3	310	123	39.7	90	29.0
4	310	175	56.5	140	45.3
5	309	223	72.2	191	61.8
Total	1,547	636	41.1	520	33.6

sion analysis were used to compute a risk score for development of systolic and diastolic hypertension for each man. The 10 variable regression analysis for systolic hypertension (adding functional class, use of digitalis, T wave findings, urea nitrogen level and serum uric acid) and for diastolic hypertension (adding time since last myocardial infarction, use of oral hypoglycemic agents, number of previous myocardial infarctions, history of angina pectoris and urea nitrogen level) did not significantly alter the outcome. The men were then ordered by quintile from low to high risk score, and the actual observed rate of development of hypertension was determined for each quintile (Table 3). There was a progressive increase in the development of both systolic and diastolic hypertension by quintile. These variables may have clinical relevance with respect to identifying people more likely to develop hypertension over time.

**Prognostic significance of baseline systolic and diastolic blood pressure elevation.** In the total cohort, men with elevated systolic blood pressure at entry into the Coronary Drug Project (baseline) had a higher 5 year unadjusted

rate of occurrence of all three end points (mortality from all causes, major coronary events and combined cerebrovascular events) than did men with a normal systolic blood pressure (Fig. 2). The *t* values of 3.66 to 4.15 for the systolic blood pressure coefficients for the univariate linear regression analysis indicate that systolic blood pressure in the total cohort was related to prognosis with *p* values less than 0.01. After control for 19 baseline variables (Appendix A), the association between an elevated systolic blood pressure and death from all causes at 5 years was reduced, but the association remained statistically significant for major coronary events and combined cerebrovascular events (Fig. 2). Men with an elevated systolic blood pressure in the corresponding *no medication cohort* had a higher mortality rate with statistically significant (*p* < 0.01) elevated systolic blood pressure coefficients for major coronary events and combined cerebrovascular events.

*Clear-cut associations were less evident for elevated diastolic blood pressure.* Univariate analyses for the total cohort showed statistically significant elevated diastolic blood



**Figure 2.** Five year event rates (per 100) related to systolic blood pressure (SYS BP), with unadjusted (solid line) and adjusted (dashed line) regression lines.  $t = t$  value for the coefficient "b" for the univariate linear regression analysis ( $y = a + bx$ ), where  $x$  is systolic blood pressure and  $y$  is the specified end point.  $t_{19} = t$  value for the coefficient "b<sub>1</sub>" for the multivariate linear regression analysis ( $y = a + b_1x_1 + b_2x_2 + \dots + b_{20}x_{20}$ ), where  $x_1$  is systolic blood pressure and the 19 other baseline variables listed in Appendix A are considered.

pressure coefficients only for the incidence of major coronary events (Fig. 3). After adjustment for 19 baseline variables, a significant association between increased diastolic blood pressure and combined cerebrovascular events also became evident. No statistically significant association between elevated diastolic blood pressure and prognosis was evident for the *no medication cohort*.

To assess further the relation of baseline hypertension to 5 year prognosis, levels of systolic blood pressures of 140 mm Hg or greater and diastolic blood pressure of 90 mm Hg or greater were used to classify the patients in the placebo group into the four subsets defined previously. Men with combined hypertension had higher unadjusted and adjusted event rates for all three end points than did normotensive men (Fig. 4). However, the higher rates were statistically significant only for combined cerebrovascular events. Men with isolated systolic hypertension had a statistically significant higher unadjusted rate for mortality from all causes than did normotensive men. The risk for men with isolated diastolic hypertension did not differ significantly from that for normotensive men for any end point. The same associations existed for the *no medication cohort*, but were not statistically significant.

**Blood pressure decrease after recurrent myocardial infarction.** Statistically significant decreases in mean systolic blood pressure (7.9 mm Hg) and mean diastolic blood pressure (3.6 mm Hg) were documented in the *definite recurrent myocardial infarction cohort* (Table 4). There were no changes in blood pressure in the year preceding the myocardial infarction (Fig. 5). These decreases persisted for at least the first year of follow-up and were unaffected by adjustment for weight reduction and development of congestive heart failure. The blood pressure reductions were sustained for 3 years in a smaller cohort of men followed up for that time period after a definite recurrent myocardial infarction. Blood pressure for the *nonmyocardial infarction cohort* remained constant over the period of 1 year before and 1 year after myocardial infarction (Fig. 5). In the cohort with *suspected myocardial infarction*, systolic blood pressure also decreased. The results were not altered when patients received antihypertensive or diuretic medication during the 2 year period (1 year before myocardial infarction and 1 year after myocardial infarction) were excluded from analysis; this analysis probably also eliminated patients with congestive heart failure.

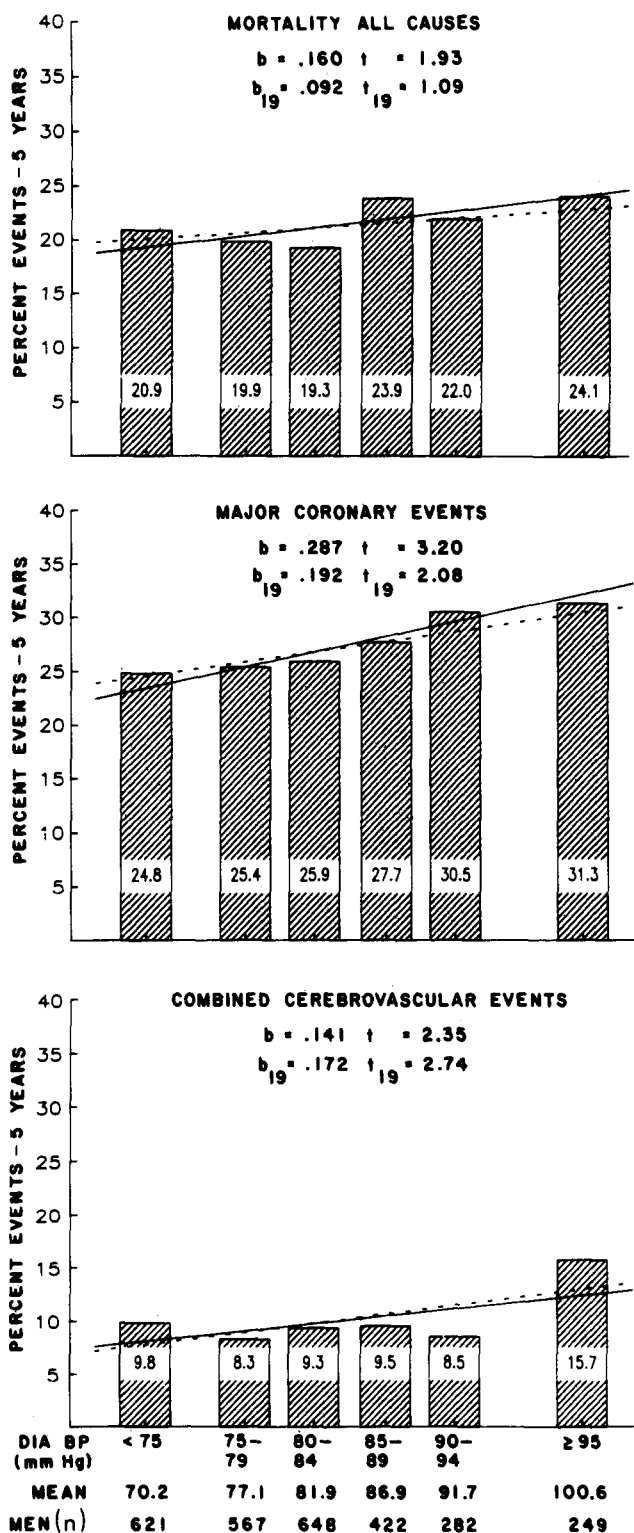
The 1 and 3 year mortality rates after recurrent myocardial infarction were approximately 2.5 times higher in the combined *definite or suspected myocardial infarction group* compared with the *nonmyocardial infarction group* ( $p < 0.01$ ) (Table 5). Patients with a decrease in blood pressure after recurrent myocardial infarction had consistently higher mortality rates than did comparable patients whose blood pressure increased or remained the same, but these differences were not statistically significant.

## Discussion

**Prognostic significance of blood pressure after myocardial infarction.** Although hypertension is a documented major risk factor for first coronary events (1-9) and pre-myocardial infarction hypertension appears to impair the long-term outlook after recovery (17), little is known about the prognostic relation between blood pressure elevation and its associated characteristics in patients *after* recovery from myocardial infarction. Limited data are available about change in blood pressure level and either disappearance or development of hypertension among survivors of myocardial infarction. Systolic and diastolic blood pressure levels in post-myocardial infarction patients are highly correlated ( $r = 0.76$ ); this has been previously reported (18) for general populations. Nevertheless, 12% of the patients have isolated systolic hypertension, a condition that appears progressively prevalent after age 60. It is common in individuals with extensive large systemic artery arteriosclerosis and, thus, is expected to be frequent in survivors of myocardial infarction.

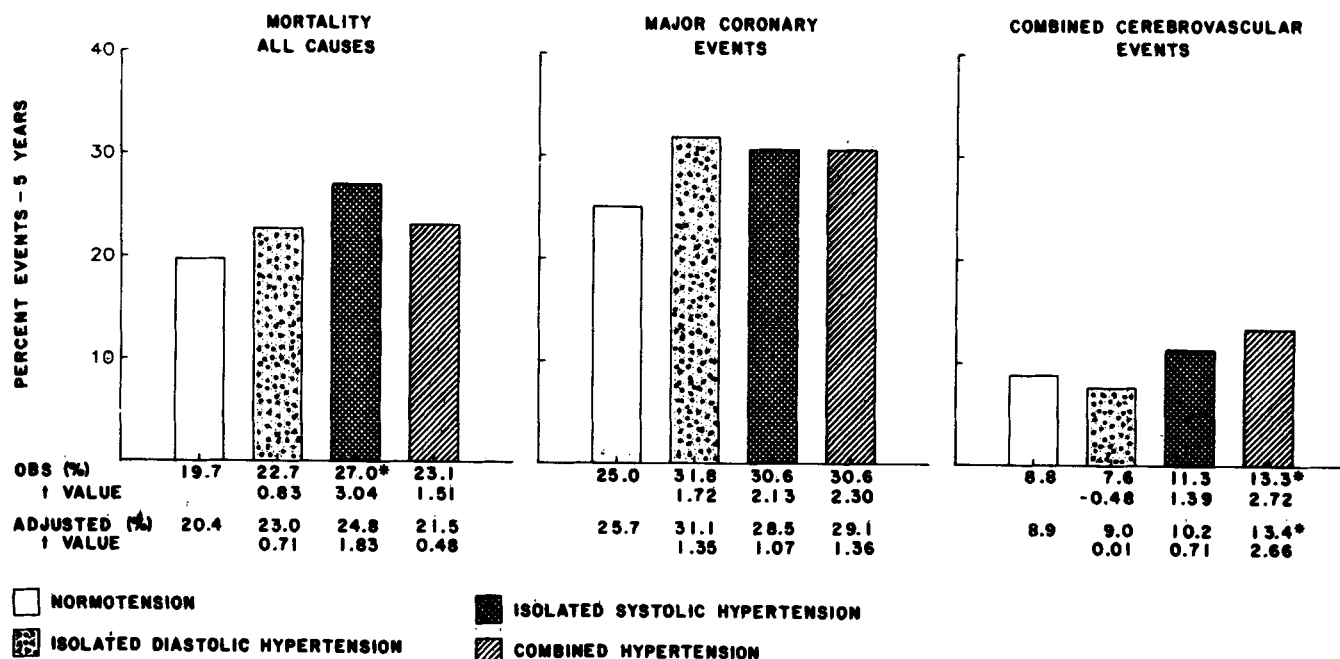
The 5 year prognosis for men with combined systolic and diastolic hypertension at baseline in the placebo group was characterized by an increase in mortality from all causes, major coronary events and combined cerebrovascular events as compared with values in normotensive men. Values were 23.1 versus 19.7%, 30.6 versus 25.0% and 13.3 versus 8.8%, respectively. The increase in combined cerebrovascular events remains statistically significant after adjustment for 19 baseline variables. The physician's interpretation of symptoms meeting the criteria for transient stroke or transient ischemic attack may have varied significantly, making these items and the combined cerebrovascular events end point a less precisely defined end point than the cardiac end points. Even after control for the 19 baseline variables, the association between an elevated systolic blood pressure and major coronary events and cerebrovascular events remained statistically significant (Fig. 2). Isolated systolic hypertension also significantly increased the risk of mortality from all causes. Because systolic blood pressure is a major contributor to myocardial oxygen demand, systolic blood pressure elevation is likely to exacerbate the clinical manifestations of myocardial ischemia and adversely affect prognosis. In a prospective epidemiologic study (8,9), isolated systolic hypertension was associated with a two- to threefold increase in mortality from all causes, as well as cardiovascular and coronary mortality in both men and women.

**Previous studies.** Many prior studies assessing the prognostic significance of blood pressure elevation after myocardial infarction were based on in-hospital determinations during the acute illness; these data cannot be compared with those of the present study. The blood pressure decrease described by Master et al. (19) in 538 patients with initial and recurrent myocardial infarction was maximal during the



**Figure 3.** Five year event rates (per 100) related to diastolic blood pressure (DIA BP) with unadjusted (solid line) and adjusted (dashed line) regression lines. Format as in Figure 2.

hospitalization; two-thirds of hypertensive patients regained their hypertension, half before discharge from the hospital and the other half within 1 to 2 years. The level of blood



**Figure 4.** Five year event rates (per 100), unadjusted observed (OBS) (bars) and adjusted for 19 baseline variables, for subsets defined by baseline systolic and diastolic blood pressures. *Normotension*: systolic blood pressure less than 140 mm Hg, diastolic blood pressure less than 90 mm Hg (1,921 men); *isolated diastolic hypertension*: systolic blood pressure less than 140 mm Hg, diastolic blood pressure of 90 mm Hg or greater (132 men); *isolated systolic hypertension*: systolic blood pressure of 140 mm Hg or greater, diastolic blood pressure less than 90 mm Hg (337 men); *combined hypertension*: systolic blood pressure of 140 mm Hg or greater, diastolic blood pressure of 90 mm Hg or greater (339 men). *t* value for comparison with normotension group, \* denotes a *p* value < 0.01 for comparison with normotension group.

pressure after myocardial infarction did not influence prognosis. Astrup et al. (20) reported on normotension persisting up to 8 weeks after myocardial infarction in 37 of 58 pre-

viously hypertensive patients, but presented no long-term data. Gibson (21) described a considerable decrease in blood pressure early after myocardial infarction, without taking into consideration the possible effects of heart failure, diuretic therapy, sedatives and narcotics.

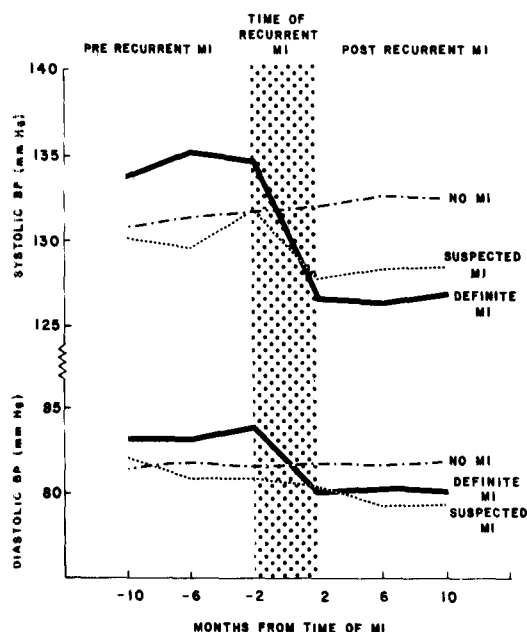
*In the Multiple Risk Factor Intervention Trial* with recruitment involving approximately 361,000 persons aged between 35 and 57 years, nearly 6,000 were immediately eliminated because they had been hospitalized for a myocardial infarction; nevertheless, they had their blood pressure and serum cholesterol levels measured and a smoking history obtained. During 5 years of follow-up, patients with myocardial infarction had a mortality rate five times that of patients without this finding; hypertension was independently related to the risk of death in this subset of patients as well as in other subsets (22).

**Table 4.** Blood Pressure Before and After Recurrent Myocardial Infarction

	Definite MI	Suspected MI	No MI*
<b>Systolic BP</b>			
Mean pre-MI†	134.7	133.1	131.7
Mean post-MI	126.8	126.9	132.0
Mean difference	-7.9	-6.2	0.3
Paired <i>t</i> value	-7.57	-3.32	0.95
<b>Diastolic BP</b>			
Mean pre-MI	84.0	81.6	81.8
Mean post-MI	80.4	80.2	82.2
Mean difference	-3.6	-1.5	0.4
Paired <i>t</i> value	-6.13	-1.20	1.66
No. of men	326	68	1,822

\*Mean values for pre- and postmyocardial infarction based on randomly selected follow-up visit. †Average 4 month time interval between pre- and postmyocardial infarction blood pressure measurement. BP = blood pressure; MI = myocardial infarction.





**Figure 5.** Blood pressure (BP) levels for three premyocardial infarction (MI) visits and three postmyocardial infarction visits for definite myocardial infarction cohort (186 men), suspected myocardial infarction cohort (58 men) and no myocardial infarction cohort (1,222 men).

It is not surprising that blood pressure elevation in survivors of myocardial infarction has prognostic significance; however, the predictive power in relative terms is less than that of hypertension in patients without myocardial infarction.

**Correlates of blood pressure after myocardial infarction.** As is the case before myocardial infarction, increasing age correlates with baseline systolic hypertension. Increased relative body weight and ST depression on the electrocardiogram were other important correlates. Elevated serum uric acid and elevated plasma glucose levels are correlates of baseline hypertension, in part as a side effect of anti-

hypertensive treatment with thiazide diuretics. More than one-fourth (28%) of the patients taking no medication influencing blood pressure at baseline began diuretic or antihypertensive medication during 5 years of follow-up. Recent general population studies (3,23,24) among white and black men and women have shown similar positive correlations between relative body weight, heart rate, plasma glucose, serum uric acid and blood pressure independent of the confounding effects of diuretic and other antihypertensive medications.

**Decrease in blood pressure after recurrent myocardial infarction and its prognostic significance.** Statistically significant decreases in both systolic and diastolic blood pressures occurred after *recurrent myocardial infarction* and persisted during at least 1 year of follow-up (through 3 years of follow-up in the smaller cohort of men followed up for this time period). The group of patients with *suspected recurrent myocardial infarction* also had a decrease in systolic blood pressure. Although not statistically significant, a decrease in blood pressure suggests a less favorable prognosis, a finding consistent with Framingham data (25). In that study, disappearance of prior hypertension after myocardial infarction was associated with a twofold increased risk of death, presumably because it reflected severe pump dysfunction. In the Coronary Drug Project, few patients had significant congestive heart failure after recurrent myocardial infarction as evidenced by use of diuretic drugs. In our study, some patients with a major decrease in blood pressure may have died before the postmyocardial infarction visit and, thus, would not be included in the analysis.

**Mechanism of blood pressure decrease after reinfarction.** The decrease in blood pressure after myocardial infarction did not result from weight loss in the patients in the Coronary Drug Project. It is also apparently not a consequence of overt heart failure. Given the poorer prognosis,

**Table 5.** 1 and 3 Year Mortality Rates After Recurrent Myocardial Infarction by Changes in Blood Pressure Pre- to Postmyocardial Infarction

	Definite or Suspected MI		No MI*	
	No. of Men	Rate (%)	No. of Men	Rate (%)
1 Year mortality	385	9.4	1,743	3.8
SBP decrease	228	11.4	722	4.3
Same or increase	157	6.4	1,021	3.5
DBP decrease	201	11.0	655	4.4
Same or increase	184	7.6	1,088	3.5
3 Year mortality	291	33.7	1,304	13.8
SBP decrease	173	37.0	551	15.2
Same or increase	118	28.8	753	12.7
DBP decrease	147	36.0	478	14.4
Same or increase	144	31.2	826	13.4

\*Values for pre- and postmyocardial infarction based on randomly selected follow-up visit. DBP = diastolic blood pressure; MI = myocardial infarction; SBP = systolic blood pressure.

or at least the trend of our data to agree with the Framingham results (25), decreased blood pressure may relate in part to damage to the heart as a pump. Possible mechanisms for the decrease in blood pressure after myocardial infarction range from loss of reflex mechanisms that elevate blood pressure to accentuation of control or modulating mechanisms.

McCall et al. (26) described a sustained decrease in systolic and diastolic blood pressures in 21 men after an initial myocardial infarction, maintained for 2 years and unrelated to weight loss. Their postmyocardial infarction blood pressure levels were greater than Coronary Drug Project premyocardial infarction blood pressure levels, allowing for a greater decrease. The correlation of serum glutamic oxaloacetic acid elevation during the acute event with decreased blood pressure suggests that this decrease is at least in part a consequence of loss of myocardial tissue.

## Appendix A

### Entry Characteristics Evaluated for Relation to Long-Term Prognosis of Middle-Aged Men Recovered From Myocardial Infarction

#### Demographic characteristics

- \*1. Age
- \*2. Race

#### Clinical characteristics

- \*3. Risk
- \*4. Number of myocardial infarctions
- \*5. Time from last myocardial infarction to entry into Coronary Drug Project
- 6. New York Heart Association functional class
- 7. History of congestive heart failure
- 8. History of acute coronary insufficiency
- 9. History of angina pectoris
- 10. History of intermittent claudication
- 11. History of intermittent cerebral ischemic attack
- 12. Use of digitalis
- 13. Use of diuretic drugs
- 14. Use of antiarrhythmic drug
- 15. Use of antihypertensive agents
- 16. Use of oral medication for hypoglycemia
- 17. Cardiomegaly on chest X-ray film

#### Electrocardiographic characteristics

- 18. Q or QS findings, or both
- 19. ST segment depression
- 20. T wave findings
- 21. ST segment elevation
- 22. Frequent ventricular ectopic beats
- 23. Ventricular conduction defects
- 24. Heart rate

#### Coronary risk factors

- \*25. Serum cholesterol
- \*26. Fasting serum triglycerides
- 27. Diastolic blood pressure

- 28. Systolic blood pressure
- \*29. Cigarette smoking
- \*30. Fasting plasma glucose
- \*31. Plasma glucose 1 hour after 75g oral load
- \*32. Serum uric acid
- \*33. Physical inactivity during leisure time
- \*34. Relative body weight
- Other biochemical characteristics
- \*35. Serum alkaline phosphatase
- \*36. Serum total bilirubin
- \*37. Plasma urea nitrogen
- Hematologic characteristics
- \*38. Hematocrit
- \*39. White blood count
- \*40. Absolute neutrophil count

\*19 adjusting variables

## Appendix B

### Diagnostic Criteria for Cardiovascular Events

The following criteria are used to diagnose cardiovascular events that occur during the follow-up period of the study.

#### 1. Recurrent Myocardial Infarction

A diagnosis of definite recurrent myocardial infarction is made if any of the following are satisfied:

- A. There is development of new abnormal Q wave findings not present on the patient's last electrocardiogram.
- B. There are clinical symptoms compatible with myocardial infarction in conjunction with serum enzyme elevation and newly developed nonspecific electrocardiographic findings (such as ST segment changes, T wave changes, ventricular conduction defects, atrioventricular conduction defects or arrhythmias).
- C. There are clinical symptoms compatible with myocardial infarction in conjunction with serum enzyme elevation without electrocardiographic findings.

A diagnosis of suspected myocardial infarction is made when there is a clinical picture compatible with myocardial infarction and either of the following conditions:

- A. There is development of new nonspecific electrocardiographic findings (such as ST-T changes, etc.), but only borderline serum enzyme elevations or enzyme studies are not done.
- B. There are no new electrocardiographic findings (or an electrocardiogram not obtained) and only borderline serum enzyme elevations or enzyme studies are not done.

The differentiation between suspected myocardial infarction and definite acute coronary insufficiency may be difficult and often arbitrary, especially in the case of ST-T changes without elevated serum enzyme levels. The investigator must exercise the best clinical judgment in arriving at a decision.

#### 2. Acute Coronary Insufficiency

For the purposes of the Coronary Drug Project, acute coronary

insufficiency signifies prolonged discomfort of cardiac origin without conclusive evidence of myocardial infarction.

*Definite acute coronary insufficiency* is reported when a patient experiences chest pain considered to be of cardiac origin lasting longer than 30 minutes and associated with no diagnostic change in Q waves but significant ST-T changes from pre-event records and with the absence of diagnostic serum enzyme levels. (It is recognized that intramural myocardial infarction as well as transmural myocardial infarction in some cases may be included in this category.)

*Suspected acute coronary insufficiency* is reported when a patient experiences chest pain considered to be of cardiac origin lasting longer than 30 minutes, but not associated with any significant ST-T wave changes (or an electrocardiogram is not obtained in connection with the event).

### 3. Angina Pectoris

A diagnosis of *definite angina pectoris* is made when there are episodes of "cardiac" pain, aching, tightness or pressure that may or may not radiate to the left neck, jaw, shoulder or arm, and: a) the discomfort is usually related to effort; b) the discomfort is relieved by rest in less than 10 minutes; and/or c) if nitroglycerin is used, the discomfort is relieved in less than 10 minutes.

*Suspected angina pectoris* is reported if the patient has pain that seems to be cardiac in origin and a, b and c are equivocal or absent.

### 4. Congestive Heart Failure

The diagnosis is made in the presence of symptoms and clinical or radiologic signs of pulmonary congestion or edema, and/or an elevated systematic venous pressure (as determined clinically or manometrically), and/or congestive hepatomegaly, ascites or peripheral edema. An associated ventricular gallop, often present, is not a required criterion.

### 5. Stroke

*Definite stroke* is reported if all three of the following criteria are met:

- A. One or more of the following symptoms and/or one or more of the following signs are present:
  1. *Carotid arterial system*: weakness or numbness in the contralateral limbs, contralateral homonymous hemianopsia, dysphasia or agnosia.
  2. *Vertebral-basilar arterial system*: weakness or numbness of single or multiple limbs, numbness of the face (particularly about the mouth), diplopia, dysphagia, dysarthria, homonymous hemianopsia, ataxia, nystagmus or altered consciousness.
- B. The above symptoms or signs persist for longer than 24 hours.
- C. Objective neurologic deficits or residua are present.

Events known to be precipitated by trauma or angiography or related to central nervous system neoplasms, abscesses and so forth are excluded.

*Suspected stroke* is diagnosed when one or more of the symptoms just outlined and/or one or more of the signs are present but are equivocal, persist for more than 24 hours, and equivocal neurologic deficits or residua are present.

### 6. Intermittent Cerebral Ischemic Attacks

*Definite intermittent cerebral ischemic attack* is diagnosed if all three of the following criteria are met:

- A. One or more of the following symptoms and/or one or more of the following signs are present with the sign or signs confirmed by physician observations:

1. *Carotid arterial system*: weakness or numbness in the contralateral limbs, contralateral homonymous hemianopsia, dysphasia or agnosia.
2. *Vertebral-basilar arterial system*: weakness or numbness of single or multiple limbs, episodes of vertigo and nausea, numbness of the face (particularly about the mouth), diplopia, dysphagia, dysarthria, homonymous hemianopsia, ataxia, nystagmus or altered consciousness.

- B. The above symptoms or signs persist for less than 24 hours.

- C. Objective neurologic deficits or residua are not present.

*Suspected intermittent cerebral ischemia attack* should be diagnosed if one or more symptoms are merely reported by the patient and there are no neurologic signs confirmed by physician observation.

### 7. Intermittent Claudication

The diagnosis of intermittent claudication is based solely on the evaluation of a carefully obtained medical history. Leg pain is diagnosed as intermittent claudication when it possesses the following characteristics:

- A. Its site must include one or both calves and/or thighs and hips.
- B. It must be provoked by walking.
- C. It must never start at rest.
- D. It must make the patient either stop or slacken pace.
- E. It must disappear on a majority of occasions within 10 minutes or less from the time when the patient stands still, and should recur after a similar interval of walking if the same pace is resumed.

### 8. Peripheral Arterial Occlusive Disease

*This definite diagnosis* is made if either of the following criteria is satisfied: a) absent popliteal or femoral pulsations, or b) diminished arterial pulses exclusive of dorsalis pedis with one or more of the following: elevation pallor, dependent rubor, prolonged return of color and venous filling after elevation or presence of ischemic ulcers.

*A suspected diagnosis* is made when diminished arterial pulses are present with the associated findings described in 6.

### 9. Pulmonary Embolism

*A diagnosis of definite pulmonary embolism* is made if the following criteria are satisfied:

- A. One or more of the following symptoms: dyspnea, substernal or pleuritic chest pain, hemoptysis; and
- B. Physical signs of one or more of the following: phlebitis, tachypnea, acute right-sided failure, shock, pulmonary consolidation, pleural friction rub; and/or
- C. Two or more of the following laboratory findings: 1) roentgenographic evidence of pulmonary infiltration, an elevated diaphragm or pleural effusion; 2) elevated serum bilirubin or lactic dehydrogenase; 3) electrocardiographic changes consistent with acute right heart strain or dilation; 4) evidence by pulmonary function studies of an increased ventilatory dead space, that is, a reduction in the mean alveolar carbon dioxide tension in the presence of a normal or nearly normal arterial carbon dioxide tension.

Alternatively, item C is satisfied if one or both of the following is available: 1) results of pulmonary isotope scanning compatible

with pulmonary embolism, or 2) results of selective pulmonary angiography compatible with pulmonary embolism.

*Suspected pulmonary embolism* is diagnosed when the available findings are equivocal or insufficient studies are carried out.

#### 10. Thrombophlebitis

A diagnosis of definite thrombophlebitis is made if both of the following criteria are met:

- A. One or more of the following symptoms are present: localized pain in the affected extremity, swelling or change of skin color of the extremity.
- B. One or more of the following physical findings are present: edema or mottled cyanosis of the extremity, a sudden increase in the circumference of the limb, differential increase in warmth of the extremity, pain in the calf and/or popliteal space or dorsiflexion of the foot (Homan's sign) or a positive sphygmomanometer cuff pain test (Lowenberg pain elicited by a cuff inflated over the affected part to a level of 60 to 150 mm Hg).

A definite diagnosis may also be made in the presence of definite or suspected pulmonary embolism and one or more of the preceding symptoms or signs.

*Suspected thrombophlebitis* is diagnosed in the presence of one symptom and equivocal physical findings.

#### 11. Atrial Fibrillation

This includes atrial flutter or fibrillation, paroxysmal or sustained, documented on an electrocardiogram.

#### 12. Other Arrhythmias

The following cardiac arrhythmias, documented on an electrocardiogram, are reported: a) supraventricular tachycardia, b) ventricular tachycardia, c) nodal rhythm, d) ventricular rhythm, e) ventricular fibrillation, f) multifocal ventricular premature beats, g) runs of three or more ventricular premature beats, and h) other major arrhythmias. Sinus arrhythmias, supraventricular premature beats and ventricular premature beats other than those just specified are not reported.

#### 13. Peripheral Arterial Embolism

*Definite arterial embolism* is documented by a history of sudden coldness, paresthesias or pain of an extremity and clinical findings of pallor, muscular weakness and loss of pulse. Angiographic or surgical findings, when available, are used to corroborate the diagnosis.

*Suspected arterial embolism* is designated when there is only a history of coldness or pain of an extremity without physician confirmation.

#### 14. Arterial Aneurysm

Definite radiographic evidence of an aneurysm is required.

#### 15. Cardiomegaly

Cardiomegaly constitutes a definite increase in heart size on comparison of two or more posteroanterior chest roentgenograms. The criterion employed by the local radiologists for determining this diagnosis is acceptable for the study. Other conditions resulting in cardiomegaly (for example, pericarditis and myocarditis) should be considered and excluded, if possible, before cardiomegaly is attributed to coronary artery disease.

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